11. Lorentzen B, Drevon CA, Endresen MJ, Henriksen T: Fatty acid pattern of esterified and free fatty acids in sera of women with normal and preeclamptic pregnancy. Br J Obstet Gynaecol 1995; 102:530-537

12. Chesley LC: Diagnosis of preeclampsia. Obstet Gynecol 1985; 65: 423-425

Cystic Fibrosis Therapy—Where We Are and How We Got There

THE DIAGNOSTIC CHARACTERISTICS of cystic fibrosis, such as meconium ileus, digestive disorders, and lung disease leading to premature death, have been anecdotally described in folk literature as early as 1650.[1] After its characterization as a distinct disease in the 1930s, cystic fibrosis was suggested to be a recessive inherited disorder.[2] The advances in the understanding of the biochemical nature of the cystic fibrosis defect and the institution of more aggressive mechanical and antibiotic therapies have been instrumental in enhancing the life expectancy and quality of life for patients affected with the disorder. Many of the affected children have now become affected adults with a host of disorders that require therapies distinct from those of the children. Whereas the mean survival age is now between 28 and 30 years, the specter of premature death from respiratory tract infection still looms on the horizon of patients with cystic fibrosis. Although the disease was initially thought to be one of the digestive tract, it quickly became evident that it was the respiratory tract infection that was responsible for more than 95% of all of the morbidity and mortality of cystic fibrosis.

It was the work by di Sant'Agnese and co-workers investigating salt depletion in cystic fibrosis children that showed excessive salt levels in the sweat of these children.[3] Those investigations set the stage for studies of the sweat glands[4] and those of the airways[5,6] some 30 years later. The findings of these studies and those of others have indicated that the basic abnormality underlying cystic fibrosis is a defect both in chloride ion secretion and in sodium absorption. Ultimately it was determined that the defect in chloride ion transport was in the apical membrane of epithelial cells[7] and that it was cyclic adenosine monophosphate-dependent.[8] Subsequent observations indicated that intact calcium- and volume-activated chloride transport pathways are present in the cystic fibrosis epithelium. These observations have been the basis of clinical trials designed to test the potential of nucleotide analogues as chemotherapeutic agents.

The underlying mechanisms of cystic fibrosis were further elucidated in 1989 by the identification and isolation of the gene most closely associated with the disease: the cystic fibrosis transmembrane conductance regulator (*CFTR*). The more than 500 mutations found in this gene have been associated with a spectrum of diseases ranging from severe pancreatic and lung disease to mild disease. It has also been determined that a previously unrelated disease, the chronic bilateral absence of the vas deferens, can result from mutations in the *CFTR* gene.[9,10]

Characterization of the *CFTR* protein has led to the development of therapies based on *CFTR* functional augmentation and on the activation of alternative ion transport pathways. In addition, the isolation of the *CFTR* gene has been the basis of one of the most intensive gene therapy efforts for any inherited disorder. The initial trials that have been designed to test the safety of a given strategy have been complicated by the host immune response.[11] This complication appears to underlie the limited efficacy and the transient expression of the *CFTR* transgene that has been observed regardless of whether the transgene is introduced by adenoviral vectors or by liposomes. These results have presented an obstacle to fulfilling the dream of a gene therapy cure for cystic fibrosis. Although the potential for cystic fibrosis gene therapy has yet to be realized, the progress toward this end has been furthered by support and initiatives by the National Institutes of Health and the Cystic Fibrosis Foundation.

Until the goal of correcting the genetic defect underlying cystic fibrosis can be achieved, the focus must be on other more conventional therapies to enhance the quality of life for adults affected with the disease. The review article by Marelich and Cross elsewhere in this issue makes this point and provides an overview of the present state of the art in the clinical management of cystic fibrosis.[12] Their coverage on the present state of intervention for the management of the cystic fibrosis disorder emphasizes the importance of maintaining an active antibiotic and mucus-clearing regimen for the treatment of all age groups of patients with cystic fibrosis. The development of the deoxyribonuclease therapy for decreasing mucus viscosity has had a substantial effect on the quality of life of cystic fibrosis patients. In addition, clinical trials of ibuprofen have shown a substantial improvement in lung function as a result of decreasing airway inflammation. This treatment will undoubtedly find itself in the mainstream of therapies for this disease in the near future.

As an adjunct to antibiotic therapies, researchers are also developing antibacterial therapies that either modify the host immune response[13] or focus directly on bacterial binding. Because the hallmark bacterium of cystic fibrosis lung infection is *Pseudomonas aeruginosa*, there has been a substantial effort characterizing the *P aeruginosa*-binding sites both in mucus and on airway epithelial cells. Furthermore, we are now gaining a better understanding of the relationship of the modulation of cytokine-mediated inflammation in cystic fibrosis patients. It is clear that the interplay between the proinflammatory interleukin (IL)-8 and anti-inflammatory IL-10 can play a substantial role in defining the inflammatory state of an infected airway.[14] The goal will now be to enhance the levels of IL-10 (which are disproportionately low in fibrocystic airways) and decrease the levels of IL-8 (which are elevated in these airways).

The development of alternative pharmacologic therapies will continue to be necessary while the issues concerning the efficacy of cystic fibrosis gene therapy are being resolved. In fact, it is possible that both gene and pharmacologic therapies can act in concert. In certain cases, a combined approach may even be more appropriate than the application of a single therapy. The severely compromised airways of an adult with cystic fibrosis may not be as responsive to gene therapy as those of an infant or a child.

Although there will continue to be some universal treatments applicable to all of these patients, physicians will increasingly need to decide on which is the best overall therapy regimen for each patient. With the advances in research studying the genotype-phenotype relationship, individual treatments based on a specific patient's mutations and phenotype are on the horizon.[10]

As we enter the next millennium, we will be challenged by important advances in medicine. Some of these advances will have a profound effect on how we treat and view disease. At the heart of these advances will be the research efforts, both laboratory and clinical, concerned with the mechanisms underlying a given disease and the amelioration of this disease. The cystic fibrosis research effort has played a substantial role in helping define the areas that will need to be explored for the development of effective therapy. In particular, the gene therapy effort in cystic fibrosis has provided insight into hurdles that must be overcome to make it an effective alternative or complement to pharmacologic therapies. In their review, Marelich and Cross stress this point and emphasize the need for continued focus on the development of mechanical and pharmacologic therapeutic intervention for the treatment of patients with this disease. Although the potential for gene therapy is great, it is still in its infancy and must go through its growing pains before that potential will be actualized.

DIETER C. GRUENERT, PhD
Gene Therapy Core Center
Cardiovascular Research Institute
University of California, San Francisco, Medical Center

REFERENCES

1. Taussig LM: Cystic fibrosis: An overview, *In* Cystic Fibrosis. New York, NY, Thieme-Stratton, 1984, pp 1-9

2. Anderson DH, Hodges RG: Celiac syndrome—V. Genetics of cystic fibrosis of the pancreas with a consideration of etiology. Am J Dis Child 1946; 72:62-80

3. di Sant'Agnese PA, Darling RC, Perera GA, Shea E: Abnormal electrolytic composition of sweat in cystic fibrosis of the pancreas—Clinical significance and relationship of the disease. Pediatrics 1953; 12:549-563

4. Quinton PM: Chloride impermeability in cystic fibrosis. Nature 1983; 301:421-422

5. Knowles M, Gatzy J, Boucher RC: Increased bioelectric potential differences across respiratory epithelia in cystic fibrosis. N Engl J Med 1981; 305:1489-1495

6. Knowles MR, Stuttes MJ, Spock A, Fischer N, Gatzy JT, Boucher RC: Abnormal ion permeation through cystic fibrosis respiratory epithelium. Science 1983; 221:1067-1070

7. Widdicombe JH, Welsh MJ, Finkbeiner WE: Cystic fibrosis decreases the apical membrane chloride permeability of monolayers cultured from cells of tracheal epithelium. Proc Natl Acad Sci USA 1985; 82:6167-6171

8. Barthelson R, Widdicombe J: Cyclic adenosine monophosphate-dependent kinase in cystic fibrosis tracheal epithelium. J Clin Invest 1987; 80:1799-1802

9. Anguiano A, Oates RD, Amos JA, et al: Congenital bilateral absence of the vas deferens—A primarily genital form of cystic fibrosis. JAMA 1992; 267:1794-1797

10. Gan KH, Veeze HJ, van den Ouweland AM, et al: A cystic fibrosis mutation associated with mild lung disease. N Engl J Med 1995; 333:95-99

11. Yang Y, Li Q, Ertl HCJ, Wilson JM: Cellular and humoral immune responses to viral antigens create barriers to lung-directed gene therapy with recombinant adenoviruses. J Virol 1995; 69:2004

12. Marelich GP, Cross CE: Cystic fibrosis in adults—From researcher to practitioner. West J Med 1996; 164:321-334

13. Tosi MF, Zakem-Cloud H, Demko CA, et al: Cross-sectional and longitudinal studies of naturally occurring antibodies to *Pseudomonas aeruginosa* in cystic fibrosis indicate absence of antibody-mediated protection and decline in opsonic quality after infection. J Infect Dis 1995; 172:453-461

14. Bonfield TL, Panuska JR, Konstan MW, et al: Inflammatory cytokines in cystic fibrosis lungs. Am J Respir Crit Care Med 1995; 152:2111-2118